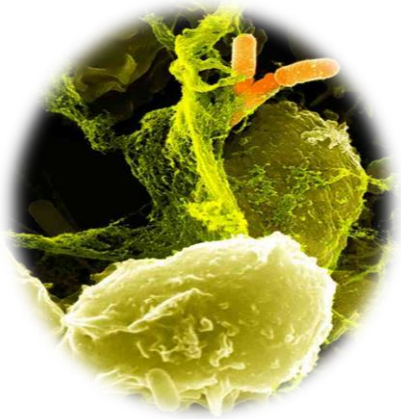
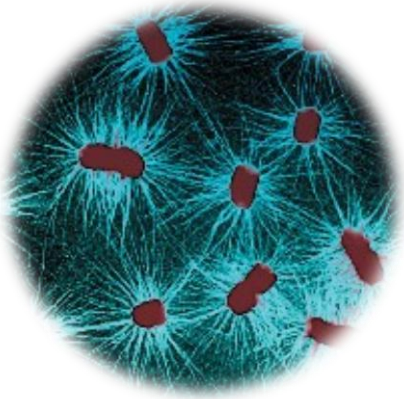
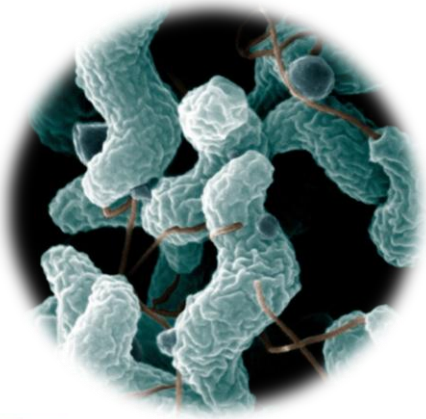
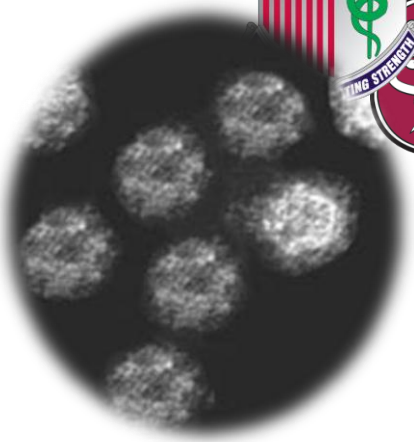

Biothreats in the Tropics

WRAIR- GEIS 'Operational Clinical Infectious Disease' Course

UNCLASSIFIED

Disclaimer

The views expressed in this presentation are those of the speaker and authors, and do not reflect the official policy of the Department of Army, Department of Defense, or U.S. Government

Acknowledgments

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Traditional Biothreat List (CDC)

Category A:

- Anthrax
- Botulinum toxin
- Plague
- Smallpox
- Tularemia
- Viral Hemorrhagic Fevers

Category B:

- Brucellosis (*Brucella* species)
- Epsilon toxin
- *Burkholderia pseudomallei* and *mallei*
- *Coxiella burnetii*
- Ricin toxin
- Staphylococcal enterotoxin B
- Typhus
- Viral encephalitis
- Water safety threats
- Food Safety threats (e.g. GNBs)

Category C:

- Nipah virus
- Hantavirus

Can be or have been used for BW or bioterrorism.

http://www.bt.cdc.gov/agent/agentlist-category.asp (Accessed 07 March 2012)

Fever in returned travelers presenting in the United Kingdom: Recommendations for investigation and initial management.

Journal of Infection (2009) 59, 1-18

Table 2 Common or important causes of fever associated with geographical areas and specific risk factors.

Risk factor	Common	Occasional	Rare but important
Geographical area			
Sub-Saharan Africa	HIV-associated infections (inc seroconversion) Malaria Rickettsiae	Acute schistosomiasis (Katayama) Amoebic liver abscess Brucellosis Dengue Enteric fever Meningococcus	Histoplasmosis Other arbovirus, e.g. Rift Valley, West Nile fever, Yellow fever Trypanosomiasis Viral haemorrhagic fever (Lassa, Ebola, Marburg, CCHF) Visceral leishmaniasis
North Africa, Middle East and Mediterranean		Brucellosis Q fever Toscana (sandfly fever)	Visceral leishmaniasis
Eastern Europe and Scandinavia		Lyme Disease	Hantavirus Tick-borne encephalitis Tularaemia
South and Central Asia	Dengue Enteric fever Malaria	Chikungunya Visceral leishmaniasis	CCHF Japanese encephalitis Other arbovirus (Nipah virus) Rickettsiae
South East Asia	Chikungunya Dengue Enteric fever Malaria	Leptospirosis Melioidosis	Hantavirus Japanese encephalitis Other arbovirus (Nipah virus) Paragonomiasis Penicilliosis Scrub typhus
North Australia		Dengue Murray Valley Q fever Rickettsiae Ross River fever	Barmah Forest Melioidosis
Latin America and Caribbean	Dengue Enteric fever Malaria	Brucellosis Coccidioidomycosis Histoplasmosis Leptospirosis	Acute trypanosomiasis (Chagas') Hanta virus Yellow fever
North America		Coccidioidomycosis Histoplasmosis Lyme disease Rocky Mounted Spotted fever	Babesiosis Ehrlichiosis West Nile fever
Specific risk factors			
Game parks	Tick typhus		Anthrax Trypanosomiasis
Fresh-water exposure		Acute schistosomiasis (Katayama) Leptospirosis	
Caves		Histoplasmosis	Rabies Ebola
HIV	Amoebiasis Non-typhoid salmonella Tuberculosis	STI, e.g. syphilis Visceral leishmaniasis	Blastomycosis dermatitidis Coccidioidomycosis Histoplasmosis Penicilliosis

Abbreviations: CCHF, Congo Crimean haemorrhagic fever; STI, sexually transmitted infections.

Causes of fever by geography, specific risks

Area/Risk	Common	Occasional	Rare but important
Sub-Saharan Africa	HIV-associated infections (inc seroconversion) Malaria Rickettsiae	Acute schistosomiasis Amoebic liver abscess Brucellosis Dengue Enteric fever Meningococcus	Histoplasmosis Arbovirus (RVF, WNV, YF,) Trypanosomiasis VHF (Lassa, Ebola, Marburg, CCHF) Visceral leishmaniasis
North Africa, Middle East, Mediterranean		Brucellosis Q fever Toscana (sandfly fever)	Visceral leishmaniasis
Eastern Europe, Scandinavia		Lyme Disease	Hantavirus, Tick-borne encephalitis Tularaemia
South & Central Asia	Dengue, Enteric fever, Malaria	Chikungunya Visceral leishmaniasis	CCHF, JE, Other arbovirus (Nipah virus), Rickettsiae
South East Asia	Chikungunya Dengue Enteric fever Malaria	Leptospirosis Melioidosis	Hantavirus JE, Other arbovirus (Nipah virus) Paragonomiasis Penicilliosis Scrub typhus

Causes of fever by geography, specific risks (cont.)

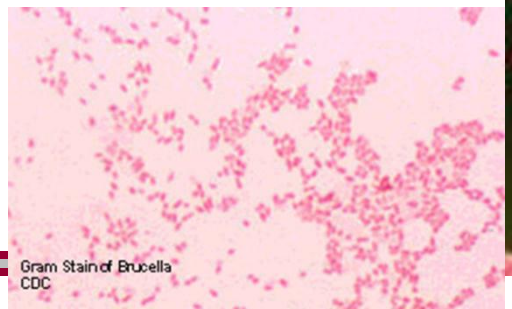
Area/Risk	Common	Occasional	Rare but important
North Australia		Dengue, Murray Valley Q fever, Rickettsiae Ross River fever	Barmah Forest Melioidosis
Latin America, Caribbean	Dengue Enteric fever Malaria	Brucellosis Coccidioidomycosis Histoplasmosis Leptospirosis	Acute trypanosomiasis (Chagas') Hanta virus Yellow fever
North America		Coccidioidomycosis Histoplasmosis Lyme disease RMSF	Babesiosis Ehrlichiosis West Nile fever
Game parks	Tick typhus		Anthrax, Trypanosomiasis
Fresh-water		Schistosomiasis, Leptospirosis	
Caves		Histoplasmosis	Rabies, Ebola
HIV	Amoebiasis Non-typhoid salmonella Tuberculosis	STI, e.g. syphilis Visceral leishmaniasis	Blastomycosis dermatitidis Coccidioidomycosis, Histoplasmosis Penicilliosis

Outline

- Brucellosis
- Q fever
- Plague
- Anthrax
- Viral Hemorrhagic Fevers (Ebola, Lassa, CCHF, etc.)
- For each: Introduction, Epidemiology, Signs and Symptoms, Diagnosis, Treatment, Prevention

Brucellosis: Introduction

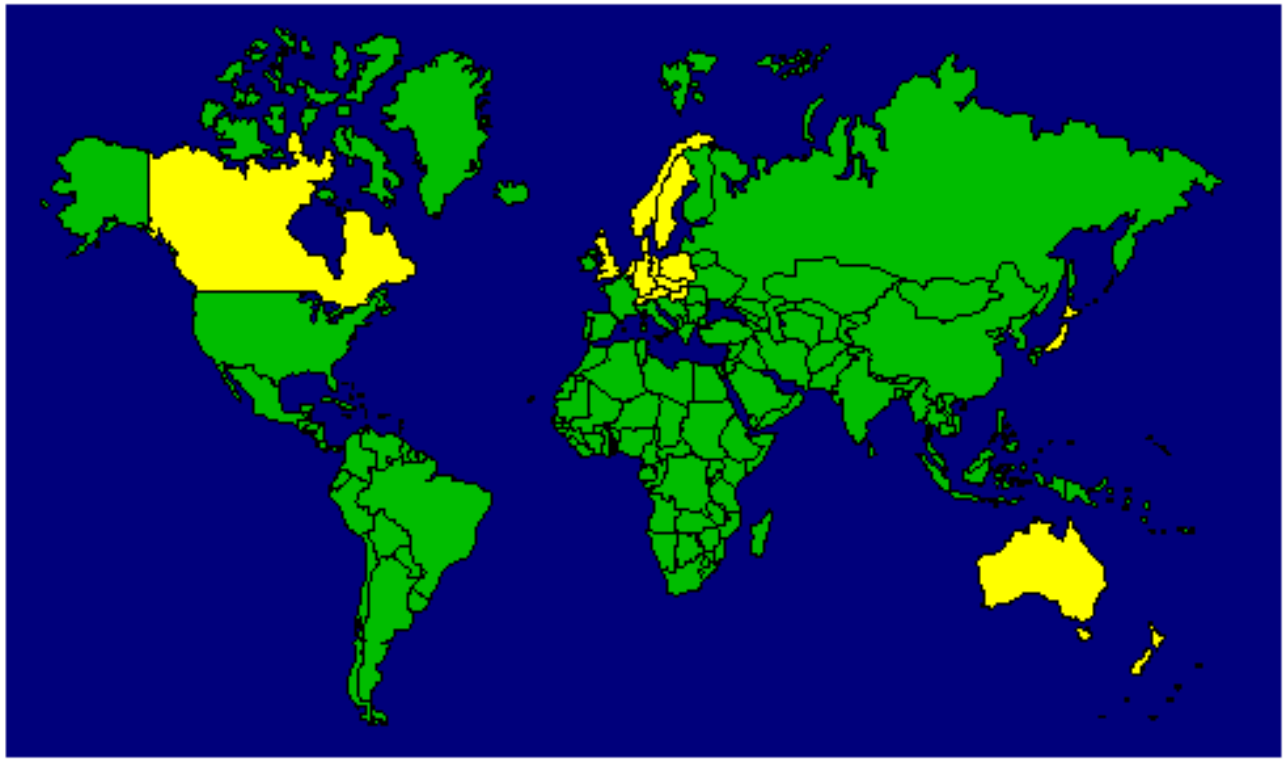
- Zoonotic infection with worldwide distribution, often acquired via consumption of dairy products from infected animals
- Economically important disease of domesticated animals
  - Infectious abortion in ruminant livestock, sterility in swine and dogs
  - Infects wild animals as well; forms a reservoir
- Protean manifestations and chronic infection in humans
- Bacteriology:
  - Small, aerobic, nonmotile, nonsporulating, Gram-negative coccobacilli
  - Slow-growing in culture
  - Intracellular pathogen


Gram Stain of Brucella
CDC

Brucella species

Species	Usual Host
B. melitensis	sheep, goats
B. suis	swine
B. abortus	cattle
B. canis	dogs
B. ovis	sheep
B. neotomae	rodents
*B. maris**	marine mammals

Brucellosis: Epidemiology



Highest prevalence: Mediterranean basin, Arabian peninsula, Central and South America (also high in Central Asia)

Brucellosis: Transmission

- Most cases acquired from infected animals
  - Dairy from infected animals
  - Occupational: veterinarians, abattoir workers, ranchers
  - Recreational: hunters
  - Lab-acquired infections
  - Human-human sexual transmission extremely rare
- Modes:
  - Ingestion of raw milk, cheese, other dairy; raw meat, liver or blood
  - Contact with infected animal/secretions
    - Parturition/abortion materials highly infectious (≤10^{10} bacteria/g); viable in placental remains ≥20 weeks
  - Aerosol transmission:
    - Inhalation: Infectious dose = 10 to 100 organisms
    - Inoculation of conjunctiva

Brucellosis: Clinical Presentation

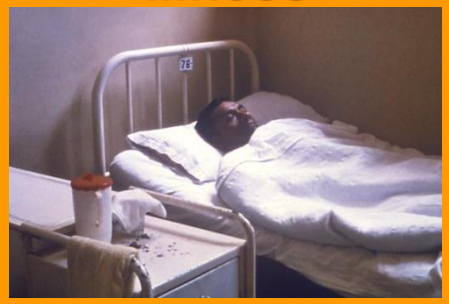
Exposure

Incubation Period

2-4 Weeks (Insidious)

- Frequently presents as fever of unknown origin (FUO)
- Symptoms often general and nonspecific

Non-Specific Febrile Illness



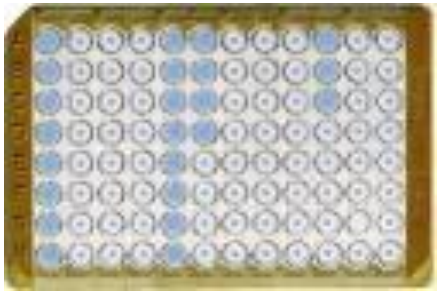
Most Common Symptoms

- Night sweats (40-90%)
- Fever (90-95%)
- Malaise/lethargy (80-85%)
- Myalgias (40-70%) – esp. of the back
- Headache, chills, anorexia
- Established infection (>2 months) often results in “undulant” fever (25-30% in endemic areas)

Brucellosis: Diagnosis

- Culture – isolation of organism for definitive diagnosis
  - May require prolonged incubation
  - Best yield from blood, bone marrow
  - Occasional culture from tissues, cerebrospinal fluid, joint aspirate, urine if focal infection
  - ******LABORATORY HAZARD******

- Serology – most common method of diagnosis
  - Standard Agglutination Test – standard globally
    - Four-fold rise or single titer ≥ 1:160
  - Cross-reaction to some other bacterial pathogens
  - ELISA – not FDA approved for human diagnosis



- PCR tests unreliable for clinical samples

Brucellosis: Treatment

- Oral antibiotics for 6 weeks
  - Doxycycline and rifampin
  - Trimethoprim/sulfamethoxazole and rifampin
  - Doxycycline, rifampin and co-trimoxazole for neurobrucellosis
- IM Streptomycin or Gentamycin
- Combined IV and oral (IV for 1st 1-2 wk)

- Post-exposure prophylaxis: 4-6 weeks of doxycycline + rifampin for high-risk lab or intentional aerosol release (not recommended for animal exposures)

Brucellosis: Prevention

- Pasteurize all dairy for human consumption
- Use proper procedure and PPE in clinical laboratories in endemic areas: BSCs, respirators
- Use fastidious hygiene in milk production
- Use proper PPE when handing livestock abortion products, treating sick animals
- Vaccine: Human vaccine is not available - even in IND
- Veterinary vaccination combined with test and slaughter for control

Q Fever: Introduction

- Bacterial disease of humans and livestock endemic almost world-wide
  - 50 cases/year in U.S.
- Bacterium that causes the disease: *Coxiella burnetii*
- Human transmission is through aerosol contact with infected animals or animal remains (fetal membranes, birth fluids, excreta) or eating or drinking raw milk and cheese

Q Fever: History in War

- ***World War II:***
  - Serbia, 1942: *Balkangrippe,* 100s of German cases
  - Italy, late 1944: 5 confirmed outbreaks (troops occupying farm buildings)
  - Grottaglie AB, Italy, 1945: 1,700 cases in U.S. airmen (presumably due to nearby sheep and goat pastures)
- ***Turko-Cypriot War:*** 78 cases in British troops, 1975
- ***OIF/OEF*** (USAPHC Q fever surveillance program): Confirmed cases among military personnel Iraq, Afghanistan; Qatar; Ethiopia since 2007

Undifferentiated febrile illnesses amongst British troops in Helmand, Afghanistan. Bailey MS et al J R Army Med 157:150-155, **2011**

From May through Oct 2008, 26 cases of "Helmand Fever" assessed and 23 diagnoses were made of which 12 (52%) were sandfly fever, **6 (26%) were acute Q fever** and 5 (22%) were rickettsial infections. Four cases had co-infections and 7 cases were not diagnosed (mostly due to inadequate samples). The clinical features and laboratory results available at the British field hospital did not allow these diseases to be distinguished from each other. The exact type of rickettsial infection could not be identified at the UK Special Pathogens Reference Unit (SPRU).

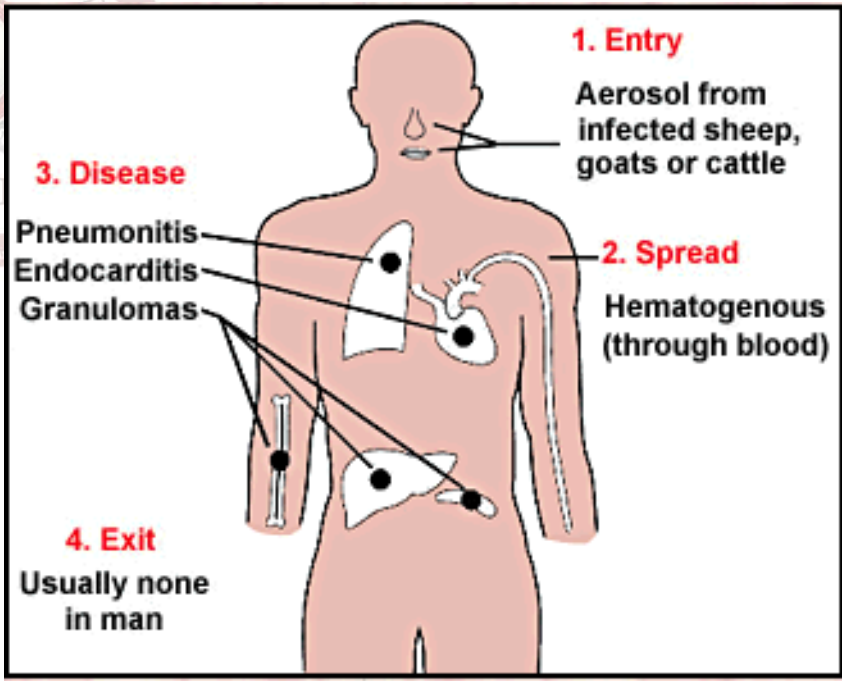
Q Fever: Human infection

- At risk:
  - Abbatoir workers, veterinarians, farmers, those around farms/farm animals
- Aerosol exposure (most common)
  - Farm vehicles on roads
  - Animal husbandry
  - Lab workers
  - OIF: sand storms, detonations/explosions, rotor wash, sleeping in an old wool factories or stables?
- Direct contact with animals (or parts)
  - Skinning infected rabbits, other animals
- Ingestion of raw milk
- Rare: percutaneous (crushing ticks), blood transfusion, autopsy, vertical (mother-infant), sexual
- Outbreak related to playing poker (cat queening under table)

Q fever (*Coxiella burnetii*)

- 3 clinical presentations (major)
  - Febrile illness: self-limited; most common
  - Pneumonia (with fever): severe HA, retro-orbital pain
  - Hepatitis (with fever): “doughnut” granulomas”
  - * 60% asymptomatic

  Complications:
  - Endocarditis
    - Culture negative; chronic
  - Optic neuritis
  - Encephalitis



Q Fever: Acute Signs & Symptoms

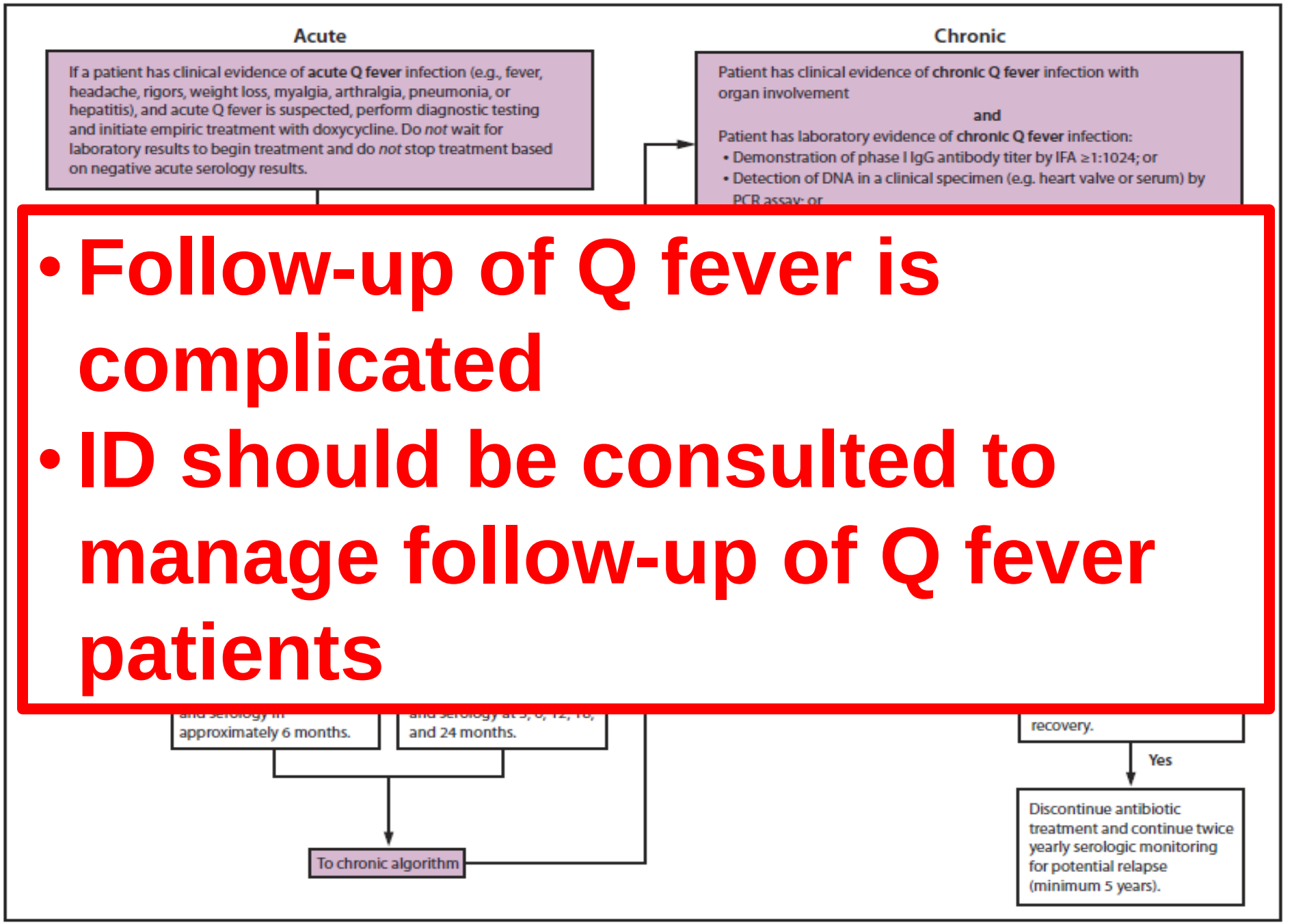
Nonspecific, febrile syndrome

Fever	99%
Weight Loss	82%
Headache	68%
Shortness of Breath	**64%**
Myalgias	54%
Cough	**51%**
Chest Pain	**45%**
Arthralgias	27%
Neurologic symptoms	23%

Q Fever: Diagnosis

- Serologic testing: Main method of laboratory diagnosis
  - Ab to phase II antigen: high in acute
  - Ab to phase I antigen: high in chronic; indicates continued exposure to agent
  - Indirect immunofluorescent antibody/assay (IFA)
    - Fourfold/greater change in IgG antibody titer to phase II antigen between paired acute- and convalescent-phase serum samples (3-6 weeks apart)
- Confirmed via other methods
  - Single positive IFA IgG titer of ≥ 1:128 to phase II antigen (with clinical correlation) defines a probable case
  - Serologic evidence of elevated phase II IgG or IgM antibody reactive with *C. burnetii* antigen by enzyme-linked immunosorbent assay (ELISA), dot-ELISA, or latex agglutination.
  - PCR available in specialized labs
  - Immunohistochemical staining of biopsy material
  - Culture from biopsy material less sensitive than serology
    - Cell (not blood) cx is possible
  - ***A significant laboratory hazard* -> Done in BSL-3 labs only**

FIGURE. Q fever management algorithm*



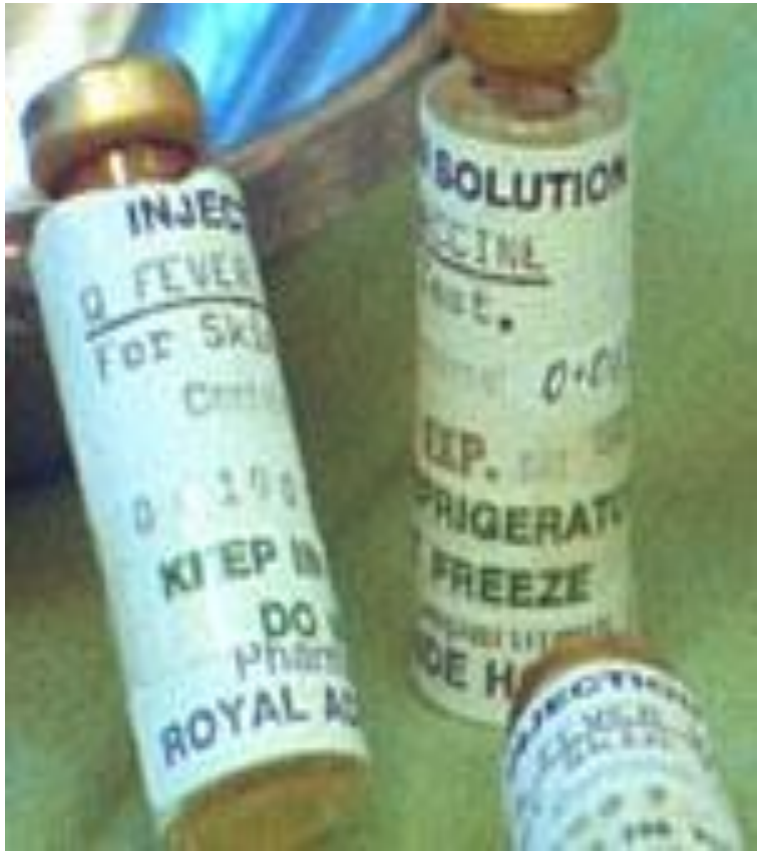
- **Follow-up of Q fever is complicated**
- **ID should be consulted to manage follow-up of Q fever patients**

Q Fever: Treatment

- 98% self-limited, but always treat if found
- Acute:
  - Doxy 100 mg po bid for ≥ 14 days, *or*
  - TCN 500 mg po qid for ≥ 14 days, *or*
  - Fluoroquinolones (14-21 days), *or*
  - TMP-SMX (14-21 days)
  - Pregnancy: TMP-SMX 160 mg/800mg po bid
  - Children <8 yrs: TMP-SMX or Macrolides
- Chronic endocarditis:
  - Doxy 100 mg BID plus Hydroxychloroquine 200 mg tid for > 18 mos until IgG & IgA levels drop to < 1:200 **OR**
  - Ofloxacin 200 mg tid for > 3 years
  - Cipro 750 BID + rifampin 300 BID
  - Possible valve replacement

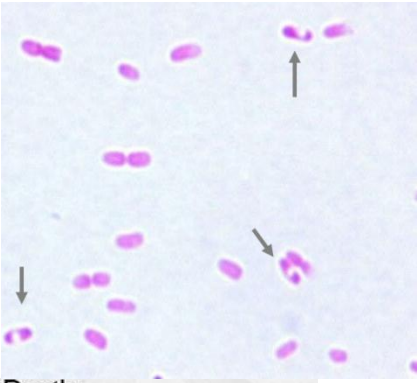
Q Fever: Prevention & Control

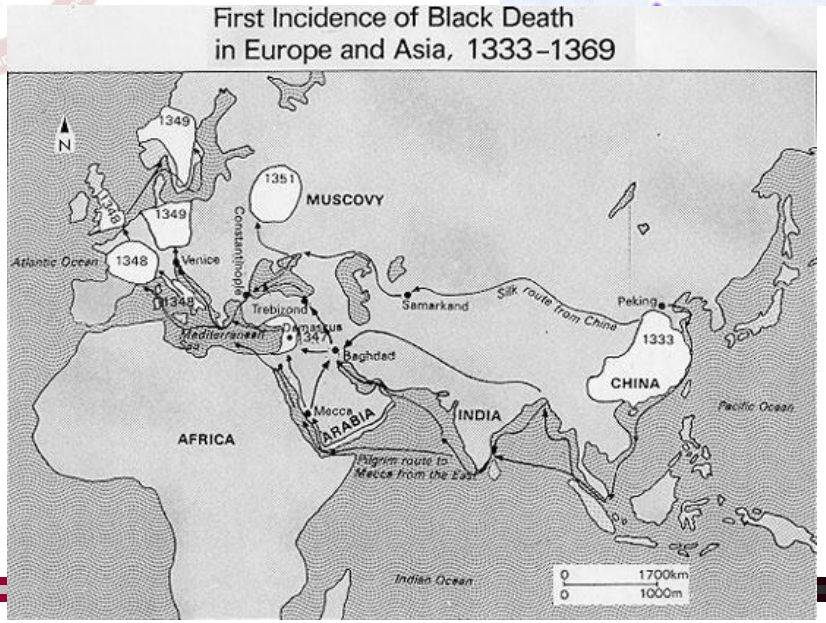
- Work with animal control to ensure infected animals are quarantined
- Killed vaccine (Q-Vax) only available in Australia and Eastern Europe
- IND vaccine available through USAMRIID
  - One dose provides > 5 yrs protection
  - Vaccine contraindicated if skin testing is positive; sterile abscesses possible in already-immune persons:
- Chemoprophylaxis: doxycycline 100 mg q12 hrs for 5-7 days



Plague: Introduction

- Historically ~200 million deaths
- Biblical (I Samuel, 5:9): "Rats appeared in the land, and death and destruction were throughout the city…young and old, with an outbreak of tumors in the groin."
- Major Pandemics:
  - 541 AD - Plague of Justinian
  - 1346 AD - 'Black Death'
  - 1894 AD - Modern Pandemic
- *Yersinia pestis*
  - Family Enterobacteraceae
  - Gram-negative, non-motile bacillus
  - Bipolar "safety-pin" staining
  - Facultative intracellular pathogen

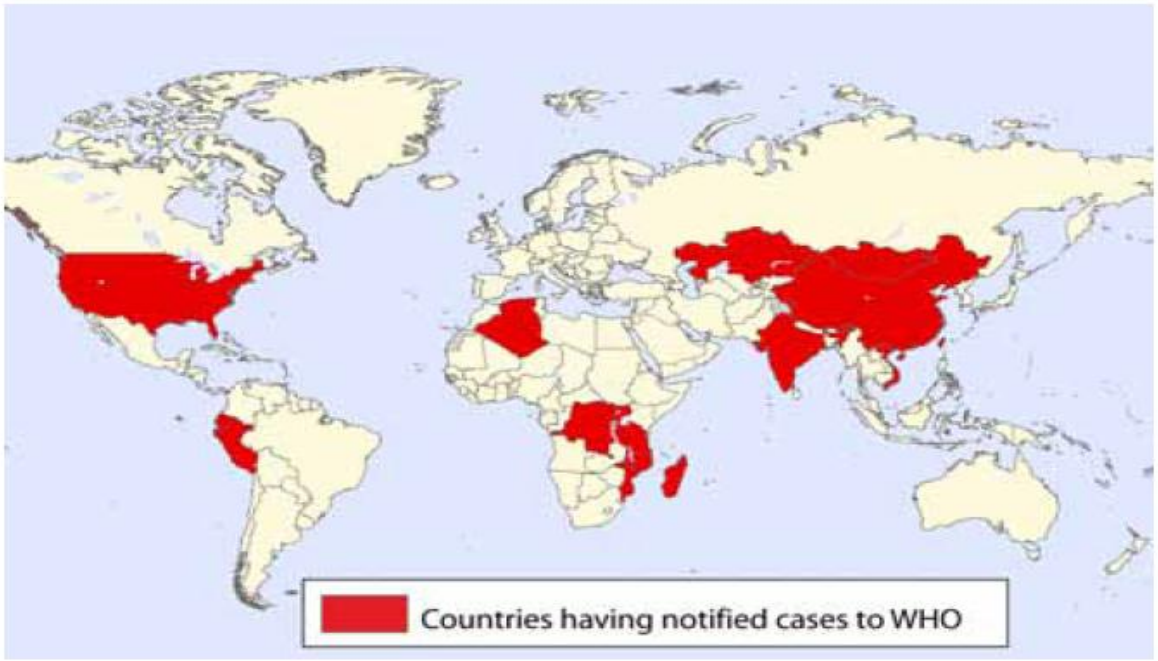




Plague: Epidemiology

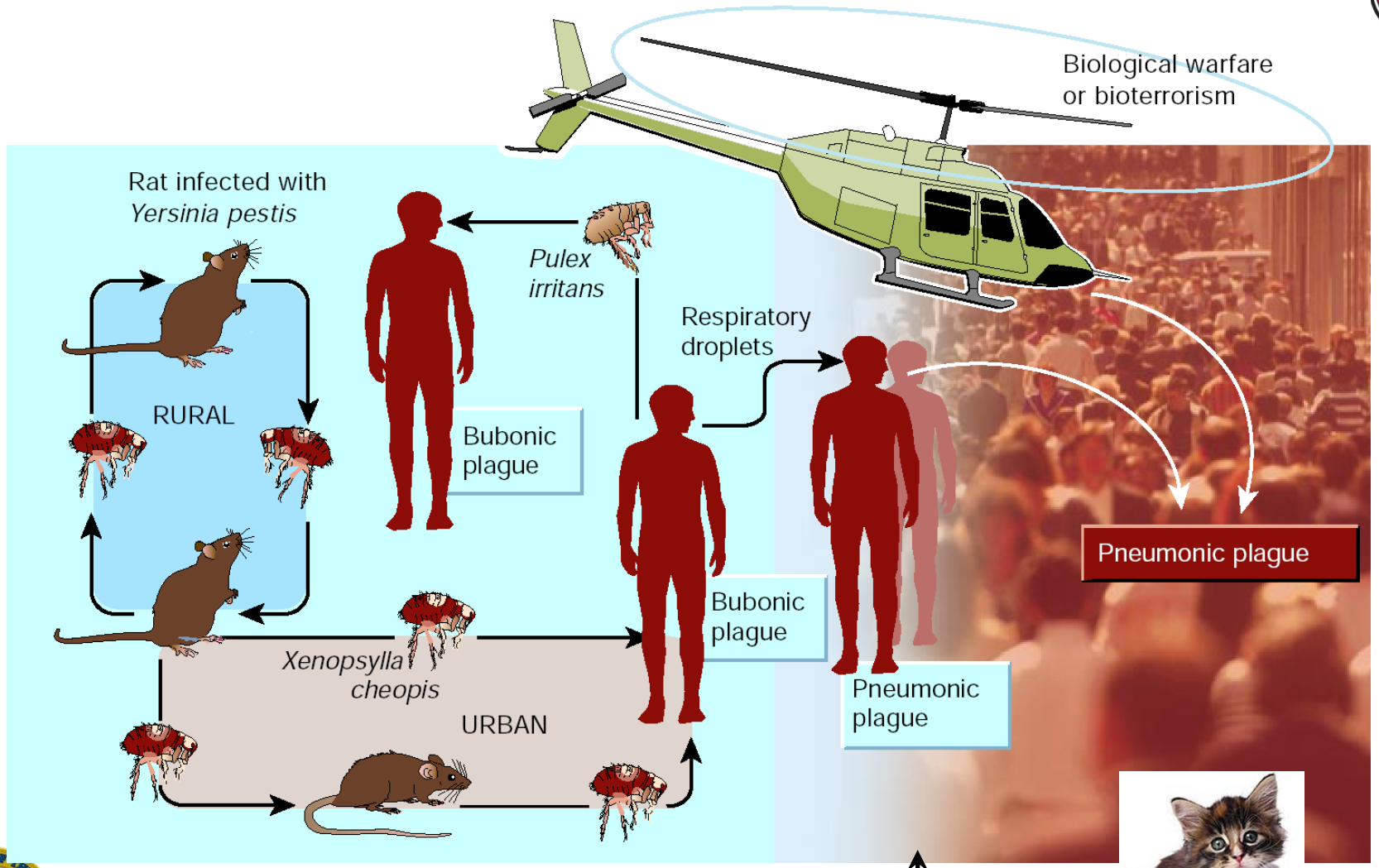
- Globally 1000-3000 cases reported annually
- Most cases reported in underdeveloped countries
- Case Fatality Rate: up to 70%

Figure 1 - Human plague cases : countries having notified to WHO, 2002-2005



Data Source: Epidemic Readiness and Interventions; Communicable Diseases (CDS); Map production: Public Health Mapping & GIS; Communicable Diseases); World Health Organization.

Plague: Transmission



Modified from NATURE|VOL 413 | 4 OCTOBER 2001 |www.nature.com

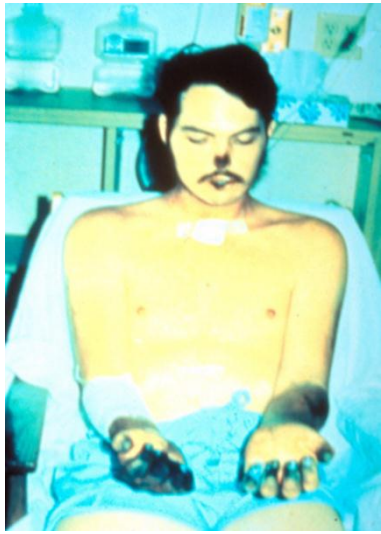
Bubonic Plague (80-95% of cases)

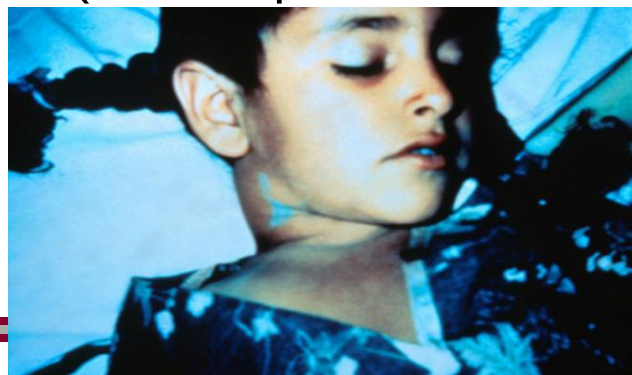
- Incubation 2-8 days (mode 3-5 days)
- Sudden onset of flu-like syndrome
  - Fever up to 40ºC (104ºF)
  - Malaise (75%), chills (40%), headache (20-85%), altered mentation (26-38%), N/V (25-49%)
  - Abdominal pain (50%)
- Bubo develops within 24 hours
  - Swollen, infected lymph node (1-10 cm size); v. painful, rarely suppurates
  - Femoral > inguinal > axillary, cervical
  - Any lymph nodes can be involved;
- Other findings
  - Papule, vesicle, eschar, or pustule = Flea bite (25%)
  - Tender palpable liver and/or spleen
  - Acute abdomen (intra-abdominal node buboes)

Mortality: 60% if untreated, <5% with prompt therapy

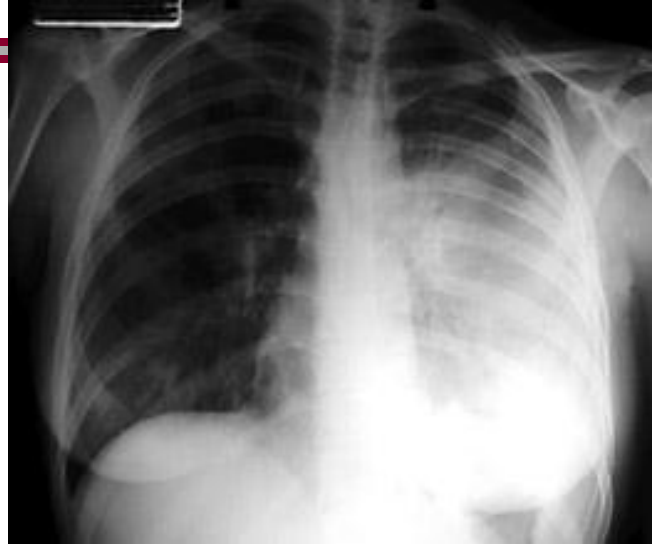
Septicemic Plague (10-20% cases)

- Secondary extension of bubonic form
  - ~25% of all bubonic forms progress
  - High density bacteremia; rapid multiplication in blood
- Primary cases possible
  - Absence of lymphadenopathy and pneumonia
- Symptoms:
  - Gram negative septicemia
    - High fever, chills, prominent gastrointestinal (nausea, vomiting, diarrhea, abdominal pain)
    - Hypotension, tachycardia, tachypnea
  - Microvascular thrombosis in small, acral vessels (low temp coagulase)
    - Purpura, necrosis, gangrene, DIC





Pneumonic Plague

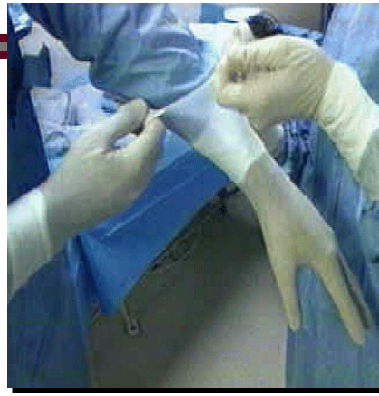


- Primary or secondary
- Incub: 1-6 days (Mean: 2-3 days)
- Acute onset
  - fever, chills, malaise +/- lymphadenopathy
- Fulminant illness
  - Rapidly advancing tachypnea, dyspnea, hypoxia, chest pain, cough, hemoptysis
  - Purulent sputum – may become blood-tinged or grossly hemorrhagic
- CXR – non-specific
- GI symptoms are often present

Plague: Treatment

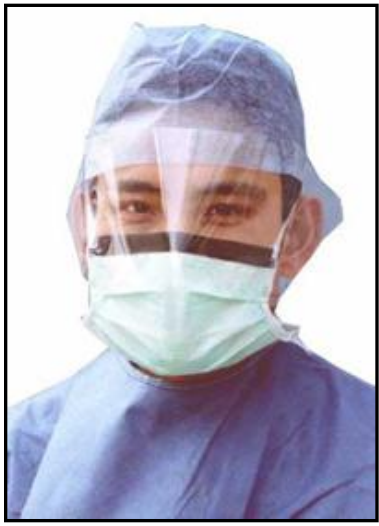
- Parenteral antibiotics recommended initially
  - Streptomycin (old favorite) 1gm IM bid, or
  - Gentamicin 5 mg/kg IV daily, or 2mg/kg loading dose then 1.7 mg/kg IM or IV q8h, or
  - Doxycycline 200 mg IV then 100mg q12h, or
  - Ciprofloxacin 400 mg IV q12h
- Switch to oral antibiotics after appropriate clinical improvement
- Duration of Rx: 10-14 days
- Meningitis – Drug of choice - chloramphenicol

Plague: Prevention



- Infection Control: Standard precautions PLUS:
  - Suspect pneumonic: Droplet precautions until pneumonia ruled out or until 48-72 hrs of appropriate antibiotics
  - Confirmed pneumonic: Droplet precautions until sputum cultures negative

MMWR 1996;45:RR-14



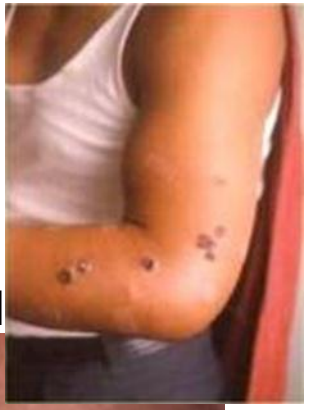
- Post-exposure Prophylaxis:

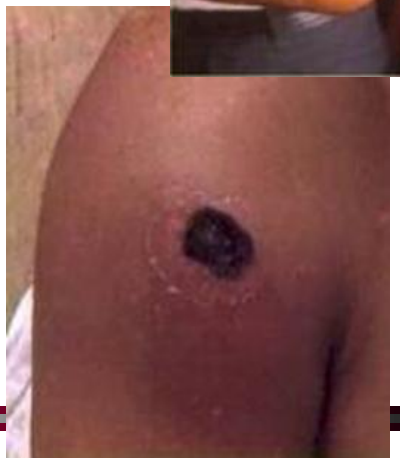
Indication	Duration	Antibiotic
Face to face contacts (≤2 meters) of pneumonic case	7 days	Preferred: Doxycycline 100 mg orally BID Alternatives: Ciprofloxacin 500mg orally BID Chloramphenicol 25mg/kg orally QID Others: Other tetracyclines, fluoroquinolones TMP/SMX if susceptibility tests allow
Suspected exposure to plague aerosol	Duration of exposure plus 7 days	

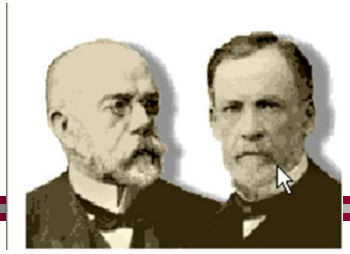
- Vaccines: Not FDA approved. IND vaccine candidates composed of *Y. pestis* F1 and V antigen developed

Anthrax: Introduction

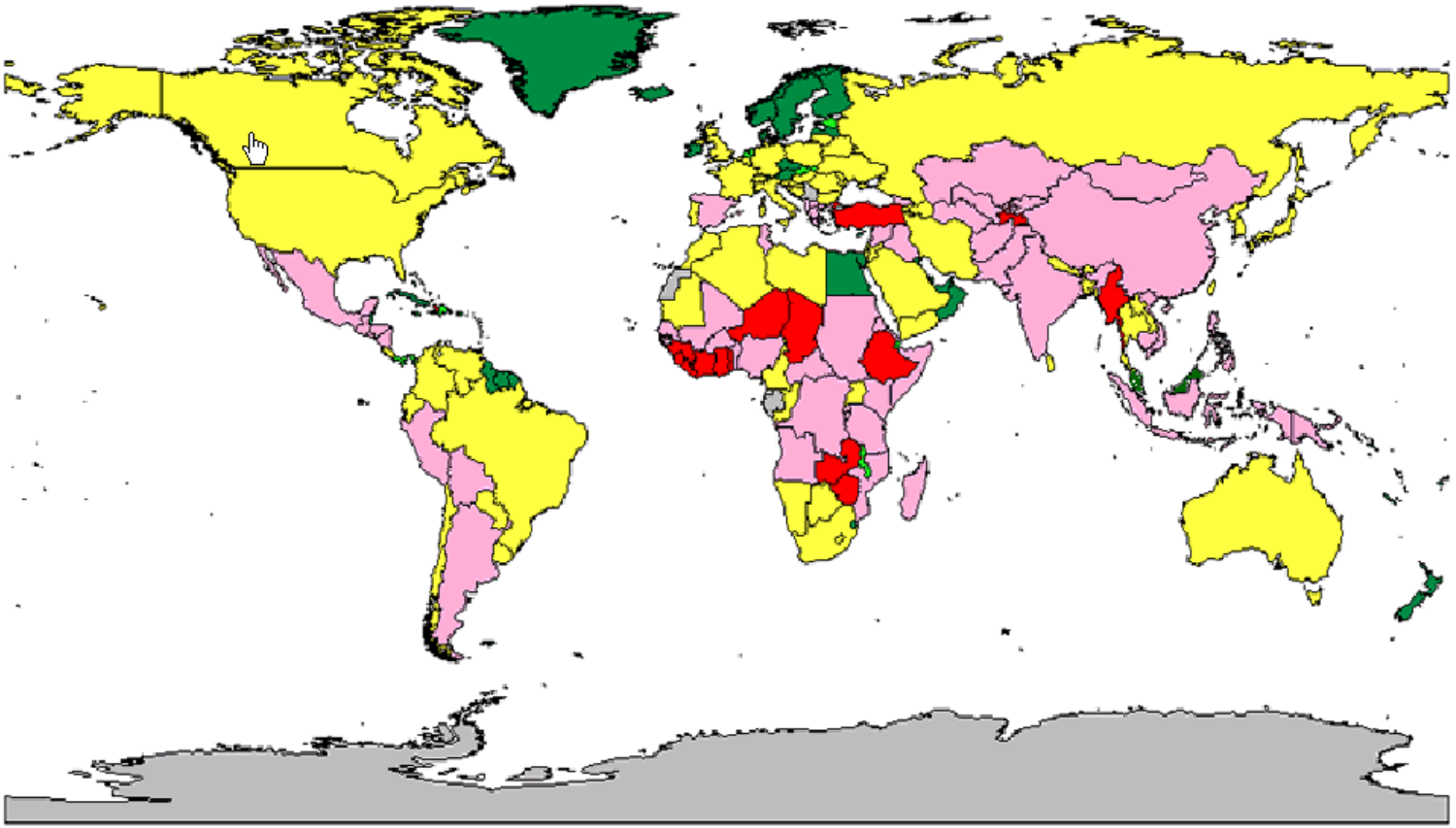
- Anthrax/*Bacillus anthracis*: from Greek for coal, anthrakis
- First clinical descriptions for animals and humans in 18th century; first disease for which microbial cause was defined (Robert Koch)
- First effective bacterial vaccine in 1881 (Pasteur and Greenfield)
- Primarily disease of herbivores; hardy spore persists in soil reservoir
- Humans usually infected (naturally) by contact with infected animals or contaminated animal products
- In U.S.:
  - ~130 cases/yr in early 1900s
  - Woolsorter's disease: inhalational anthrax
  - Before the 2001 "Amerithrax" attacks of, 18 cases of inhalational anthrax reported in the 20th century
  - Last naturally-occurring inhalation case in 1976
- Easily cultivated & stabilized, thus easily weaponized





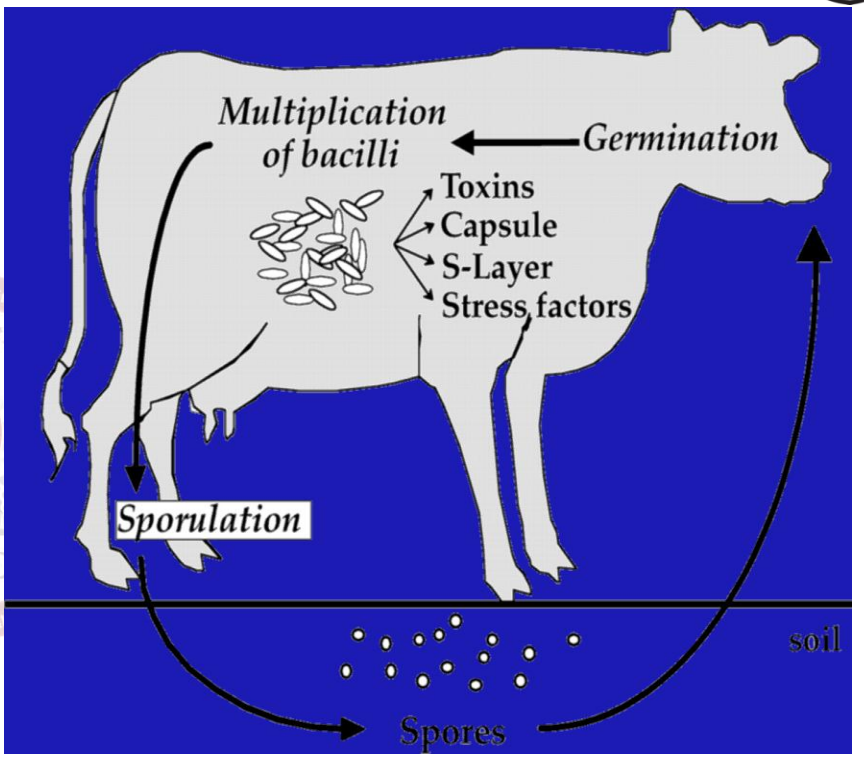


Anthrax Epidemiology



Anthrax: Transmission

- Spores are the infective form
- *B. anthracis* bacilli (vegetative cells) are shed by the dying animal and sporulate on contact with O_2, resulting in soil contamination.
- Risk Groups:
  - Farmers, ranchers/shepherds
  - Wool mill workers
  - Tannery, bone meal workers
  - Drum makers (natural hide) or players
  - Laboratory workers
  - Military personnel



Anthrax life cycle

Anthrax Case Definition

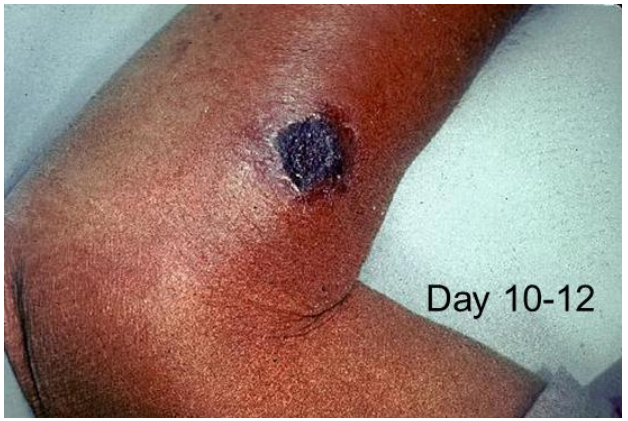
- Acute onset, distinct clinical forms:
  - Cutaneous: skin lesion evolving in 2-6 days from a papule, through a vesicular stage, to a depressed black eschar
  - Inhalational*: brief prodrome resembling a viral respiratory illness, followed by development of hypoxia and dyspnea, with radiographic evidence of mediastinal widening
  - Intestinal: severe abdominal distress followed by a fever and signs of septicemia
  - Oropharyngeal: mucosal lesion in oral cavity or oropharynx, cervical adenopathy & edema, fever

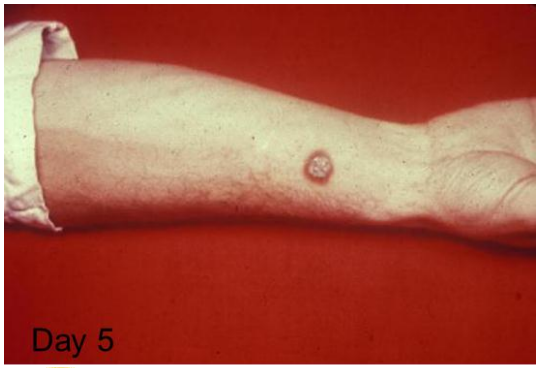
*Presentation may vary in the context of bioterrorism

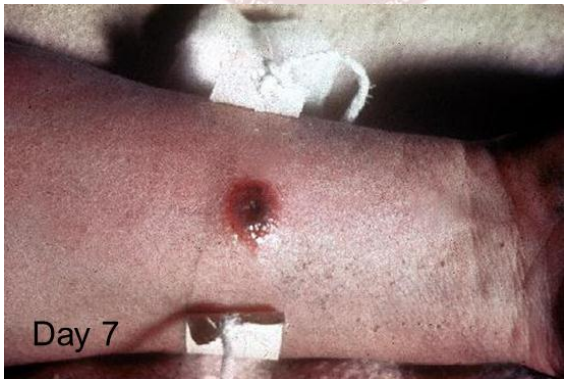
MMWR 1997;46(RR-10)

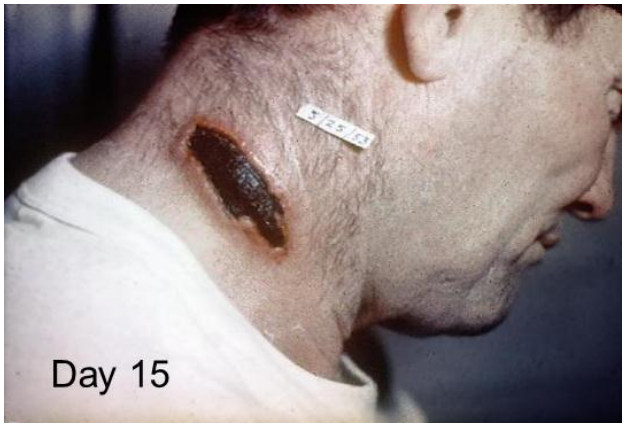
Cutaneous Anthrax

- Most common form (95%) under natural conditions
- Portal of entry: break in skin
- Incubation: hours - 12 days
- Papule → vesicle → ulcer/painless eschar
- Significant edema surrounding the lesion, and in nearby lymph nodes
- Fever, malaise, headache may be present
- Death 20% untreated; rare if treated









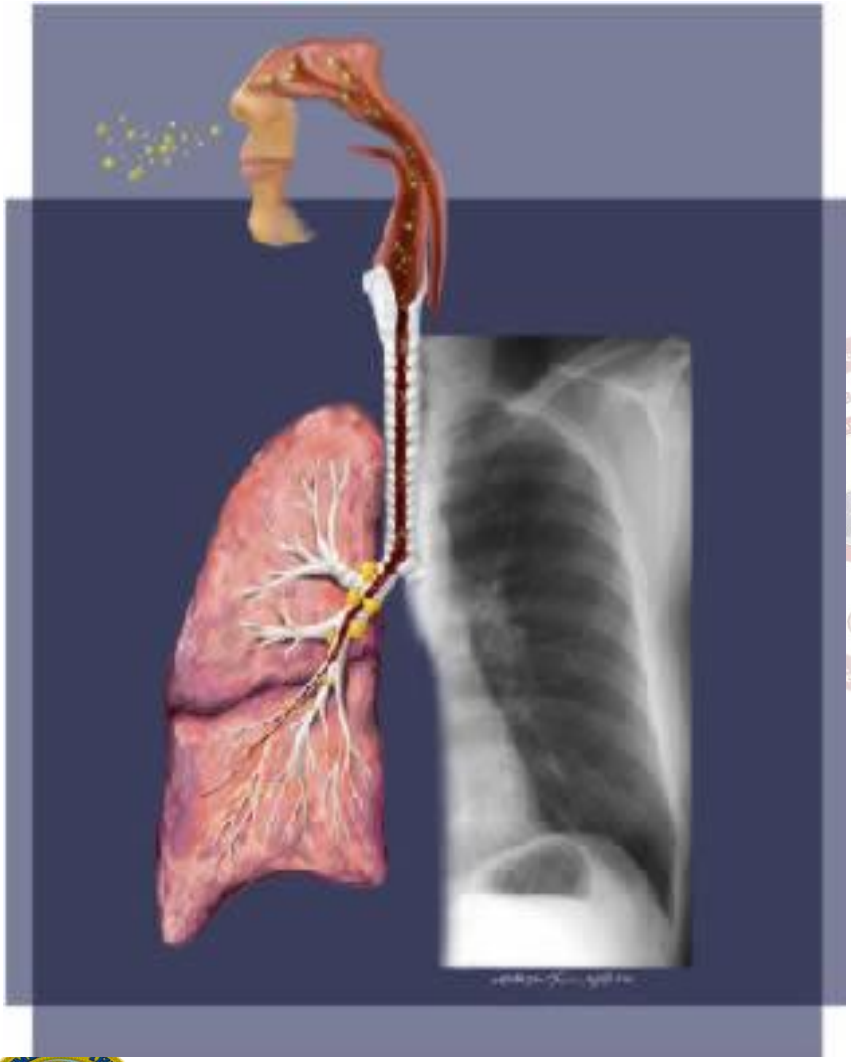
Gastrointestinal Anthrax

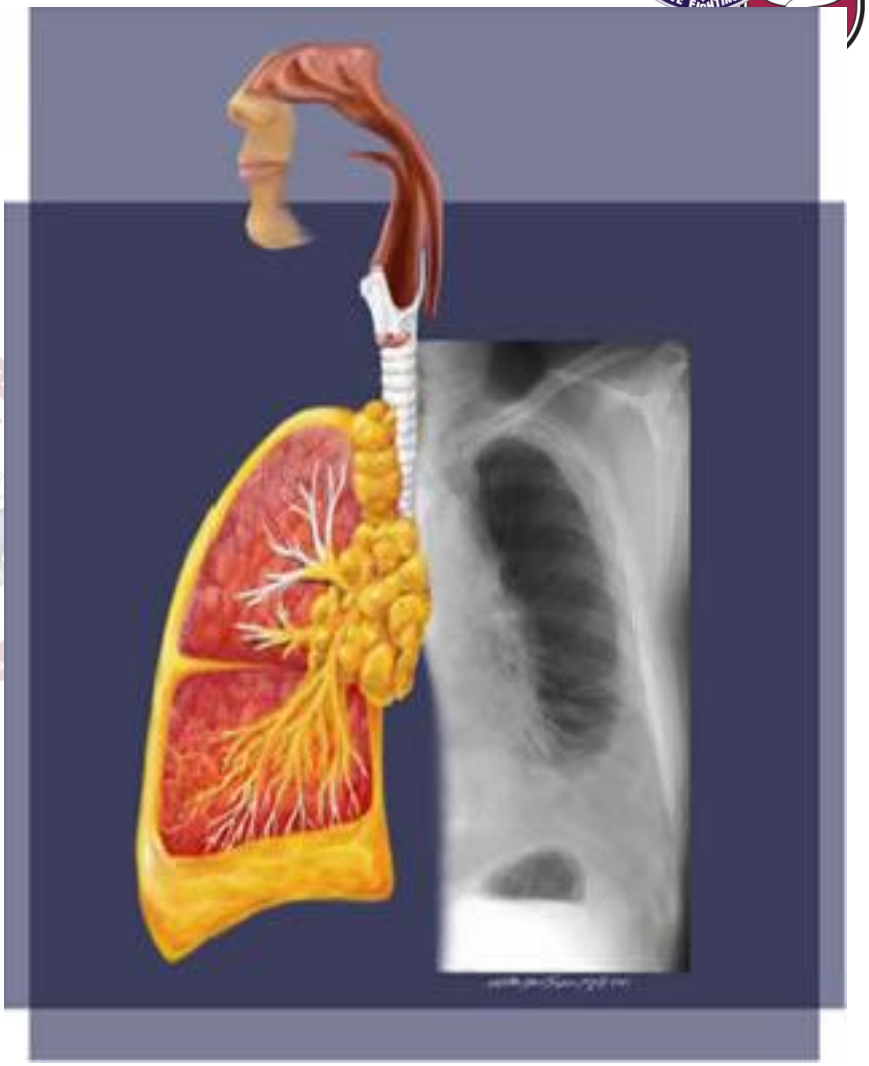
- RARE, naturally-occurring disease
- Ingestion of insufficiently cooked, contaminated meat (vegetative bacilli?)
- Probably requires a large inoculum of organisms
- Incubation period 1-6 days
- Symptoms- nausea, vomiting, fever, abdominal pain -> hematemesis, bloody diarrhea or melena and massive serosanguinous ascites
- Pathology- ulcerative lesions of terminal ileum, cecum, with hemorrhagic mesenteric adenopathy
- Hematogenous spread via direct extension from GI lumen leading to bacteremia and septicemia
- Mortality~50%

Inhalational Anthrax

- Incubation period: 1 to 43 days or longer; may be related to dose and host factors
- Initial symptoms typically appear in 2-5 days
  - Nonspecific: fever, dry cough, chest discomfort, muscle aches, malaise, profound fatigue, sweats
  - Gastrointestinal symptoms
- Late symptoms
  - Hemorrhagic mediastinitis, dyspnea
  - Some cases develop meningitis
  - Rapid progression to shock, death
- Mortality rate 100% despite aggressive Rx in “advanced disease” but is lower with early treatment; 6/11 cases in the 2001 outbreak survived with early aggressive therapy

Inhalational Anthrax





Anthrax: Diagnosis

- Isolation of *B. anthracis* from a clinical specimen
  - Blood, lung fluid, spinal fluid, skin lesion **OR**
- Positive serology* (after symptom onset) **OR**
- Demonstration of *B. anthracis* in a clinical specimen by immunofluorescence (DFA for cell wall and capsule)*
- Nasal swabs & serology – not useful for clinicians, but can help determine the extent of exposure in an epidemiologic investigation

*testing at state public health labs or CDC

MMWR 1997;46(RR-10)

Cutaneous Anthrax: Treatment
(without systemic symptoms)

CFR – 20% untreated; <5% treated

1. PO Antibiotics (adult doses)
    1. Natural exposure:
        - 7-10 days PO antibiotics
    2. Associated with potential BW aerosol attack:
        - Ciprofloxacin 500mg PO q12hr for 60 days, or
        - Doxycycline 100mg PO q12hr for 60 days*
2. NSAIDS/Steroids for severe edema?
3. Infection control:
    - Contact precautions
    - Do not debride lesions

*Until susceptibilities known.
- May switch to Amoxicillin po
- Avoid DOXY in pregnancy and in children <8yr

Inhalational Anthrax: Treatment

- Ciprofloxacin or doxycycline
  - Fluroquinolones with similar activity and CNS penetration preferred over doxycycline
- One or two additional antimicrobials with adequate CNS penetration and expected *in vitro* activity
  - e.g. rifampin, vancomycin, penicillin, ampicillin, meropenem
- Clindamycin recommended due to ability to inhibit protein synthesis
- 60 day course
- Switch to single PO med upon improvement
- May have to use PO antibiotics in mass casualty situation

•Avoid Doxy in pregnancy, children under 8yr old
•Same antibiotic regimen for **GI anthrax** or **septic cutaneous anthrax**

Anthrax: Prevention

- Infection Control:
  - Standard precaution for inhalational anthrax - not transmissible person to person
  - Cutaneous anthrax RARELY transmitted - some recommend contact precautions
  - 0.5% hypochlorite solution for cleaning
- Postexposure prophylaxis (CDC recommends):
  - 60 days of oral antibiotics (Ciprofloxacin, Doxycycline, Procaine Penicillin G and Levofloxacin) +
  - 3 doses of anthrax vaccine adsorbed (AVA) at 0, 2 and 4 weeks (IND protocol or an Emergency Use Authorization)
- Vaccine: Anthrax Vaccine Adsorbed (AVA-Biothrax)
  - Licensed by Food and Drug Administration (FDA) since 1970
  - AVA now given IM at 0 and 4 weeks and 6, 12, and 18 months

Case #1A

- 35yo USMC medic in Iraq x 7 months
- En route CONUS – fever 104°F
- Now daily fever/chills + retro-orbital HA, lower back and bilateral calf pain
- ROS: sore throat, watery diarrhea x 6 days
- Exposures: insect bites, slept in revamped Iraqi chicken factory, goats roaming, walked in brackish water, ate local Iraqi-prepared food

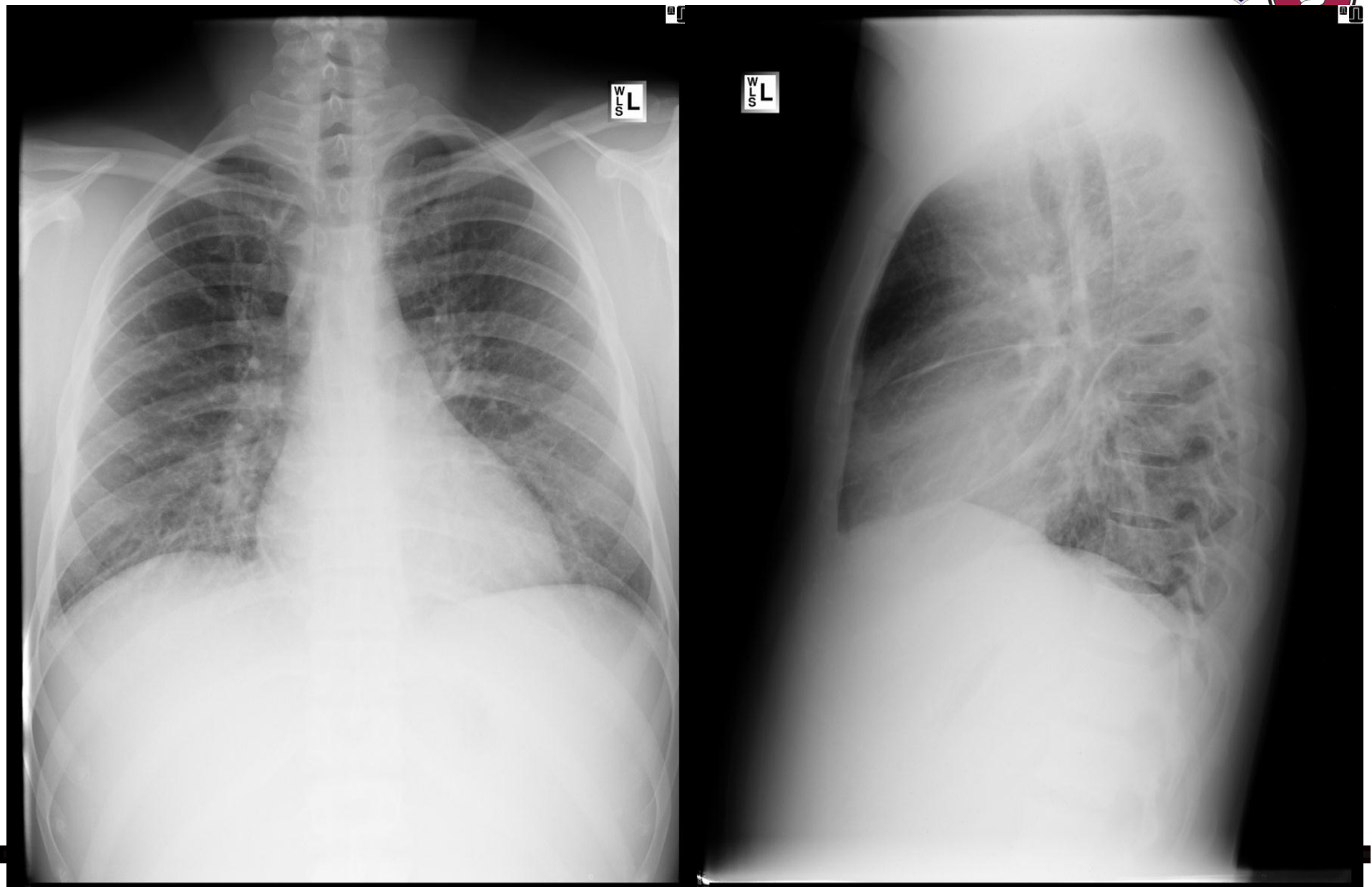
Case #1A

- Physical Exam:
  - T-103°F, HR-90, BP-110/60, O_2 Sat-99% (RA)
  - Unremarkable
- CXR, abdominal CT both normal

Case #1B

- 23yo USMC – becomes ill 3 days after #1
- Similar fever, chills, sore throat, diarrhea
- ROS: blisters on feet (waded through sewage); only ate MREs, did not sleep in chicken factory (500yds away)
- PE: T-106°F, HR-104, BP-120/70, O_2 Sat - 98%
  - Mild jaundice o/w normal

Case #1B



Case 1: Lab data

Case 1A

- **Na-130** (137-145)
- **K-3.0** (3.6-5.0)
- **Alkphos**-310 (36-126)
- **AST-125** (17-49)
- **ALT-130** (7-56)
- **Tbili 1.8** (0.2-1.3)
- WBC 4.5 (4.0-11.0) 74N/E2
- Plt-120 (150-450)

Case 1B

- **Na-130**
- **K-2.9**
- **Alkphos-137**
- **AST-173**
- **ALT-131**
- **Tbili-2.8**
- WBC-4.8
- **Plt-45**

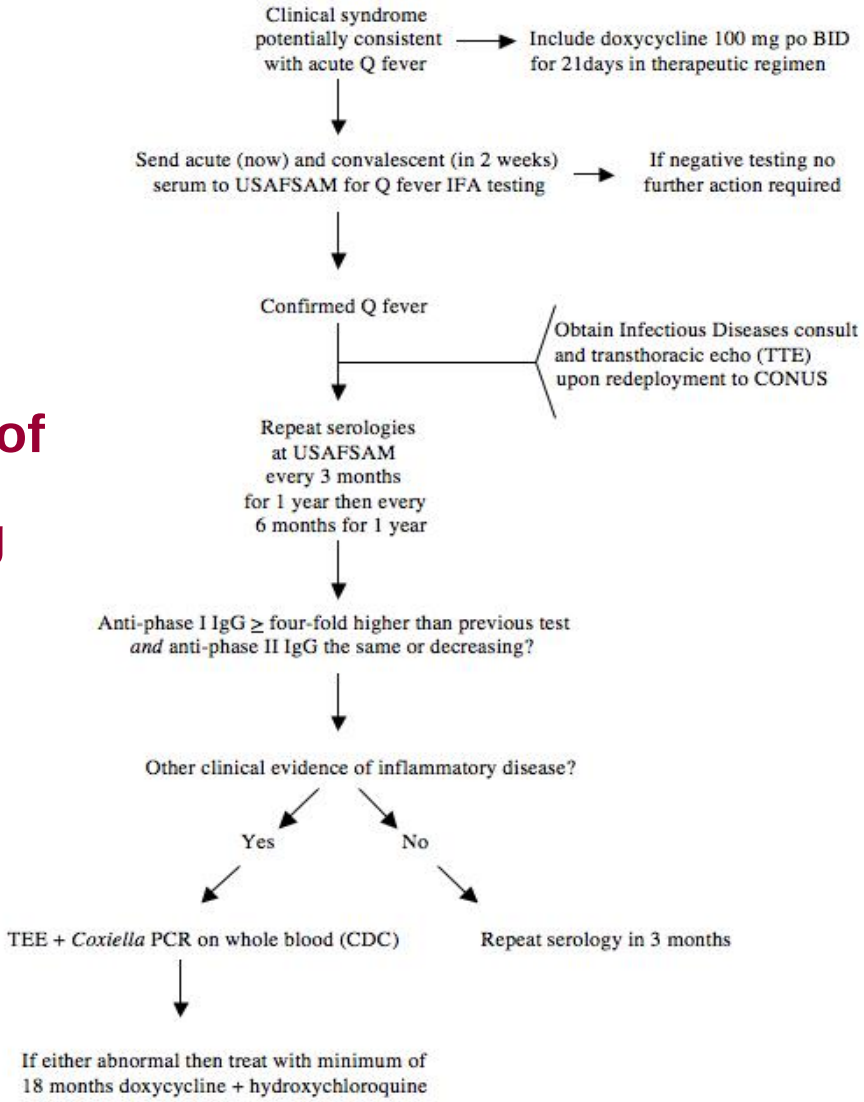
Case #1

- Differential Diagnosis:

- Malaria smears (-)
- Blood, stool, urine cultures (and CSF #1) (-)
- Acute HIV, RPR (-)
- Viral, Dengue, Hepatitis A/B/C (-)
- Leptospirosis Ab (-)

- **Q fever**

Current Recommendations of the Tri-Service Infectious Diseases Q Fever Working Group



Fevers, sweats, weight loss, chest pain, elevated erythrocyte sedimentation rate, C reactive protein, liver-associated enzymes, white blood cell count, rheumatoid factor

Case 2: Scenario*

- 37 year old man admitted to hospital because of 3 weeks of intermittent fever, abdominal and back pain
- In good health 7 months prior when started a 4-month trip by land from his native Peru to the US
- About 1 month into his trip had a fever for 10 days in Guatemala, subsided without intervention

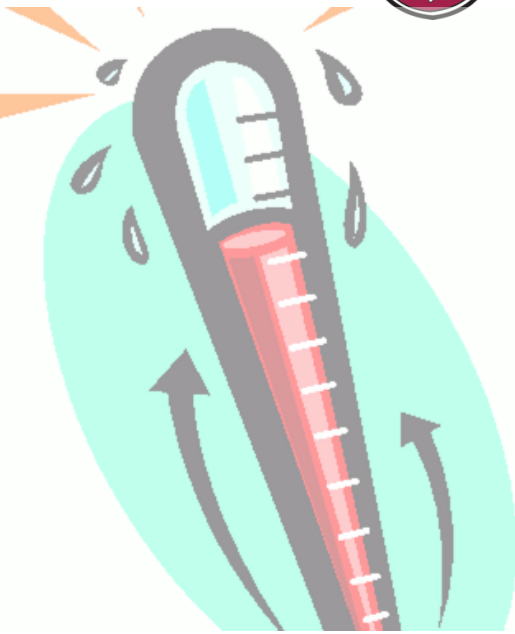
*Case Records of the Massachusetts General Hospital. NEJM Vol. 347, No. 3 July 18, 2002.

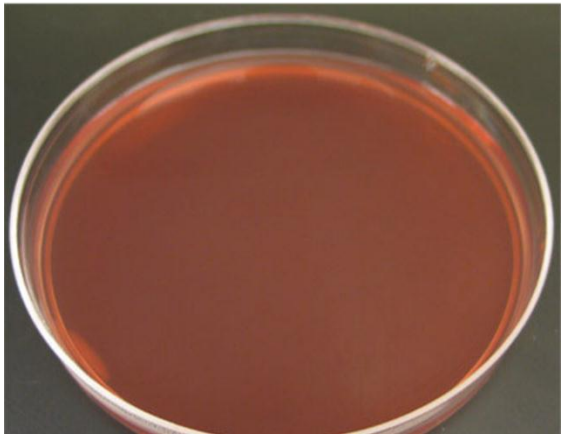
Case 2: history

- Exposures:
  - On trip ate fruit directly from trees, had milk from local sources, bathed and drank water from rivers, passed through rain forests, was bitten by many mosquitoes.
  - Had several episodes of diarrhea and fever during 4 month journey for which he was given some antibiotics.
- Course:
  - Six weeks before admission, had “burning” epigastric pain with no radiation and no change in appetite.
  - Three weeks before admission, this pain started to shift to the LUQ, left shoulder, and left part of his back. He also started having intermittent fevers, night sweats, rigors, and black stools.
- Additional info:
  - Occupation: carpenter
  - Sexual history: monogamous with wife, no other sexual exposures
  - Some exposure to animals during his journey (goats, sheep, cattle)
  - No jaundice, arthralgia, anorexia, vomiting, hematemesis, cough, or dysuria

Case 2: data

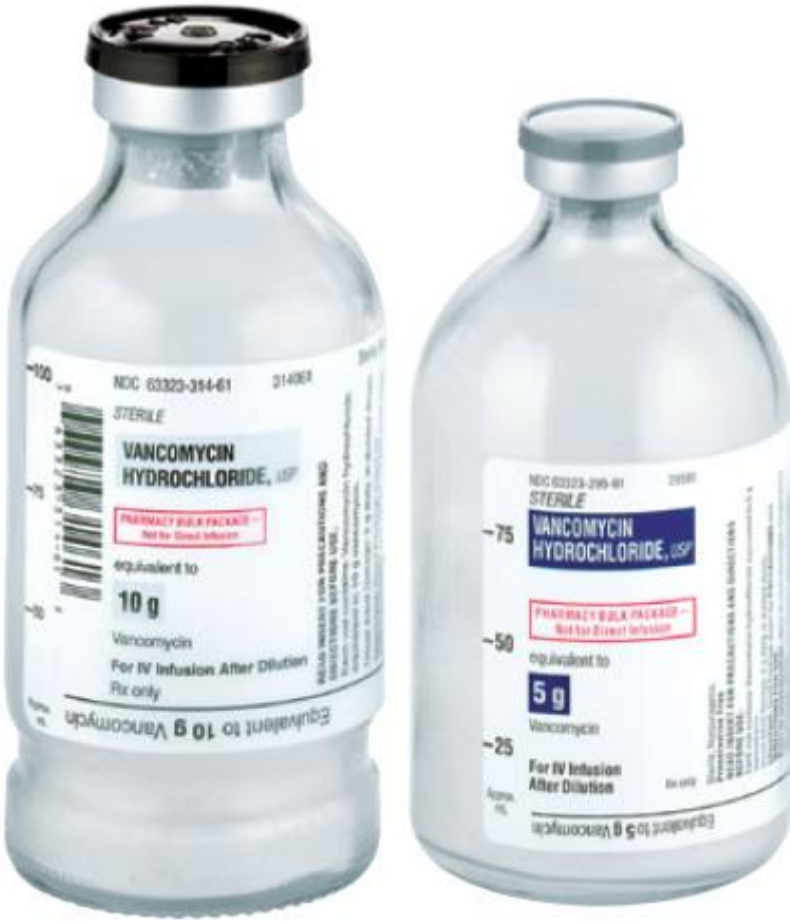
- Physical Exam
  - Temperature: 104°F (40°C) , pulse 90, respirations 18, BP 120/80
  - Patient fatigued but not acutely ill
  - A grade 2 precordial systolic murmur with no radiation
  - 2 hypodense splenic lesions
  - HEENT, Pulm, GI, GU, Derm exams all normal
- Lab results
  - Chemistry panel: normal
  - LFTs: normal
  - CBC: anemia
  - Blood cultures: no growth
  - Urine culture: no growth





Case 2: Initial Treatment

- IV vancomycin and gentamicin
- After 5 days in hospital patient felt better and was discharged
- Afebrile for 1 week after discharge, then daily temperature spikes (101-102°F), chills and shaking at night, lymphadenopathy

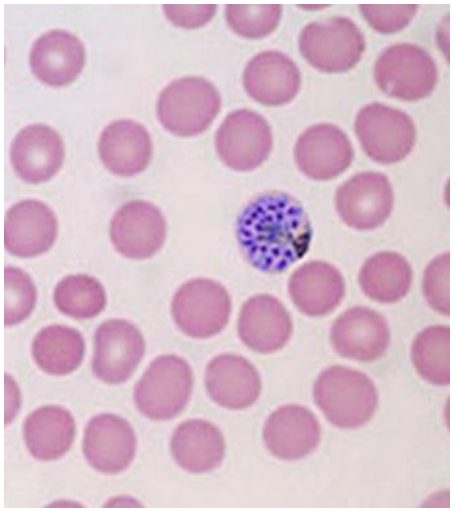


Case 2: Differential Diagnosis

- Fever, anemia, nonspecific constitutional symptoms, and abdominal/back pain, lymph nodes
- Possible infectious
  - Parasitic
  - Protozoal
  - Fungal
  - Viral or rickettsial
  - Mycobacterial
  - Bacterial
- Possible noninfectious: immunologic and idiopathic granulomatous diseases

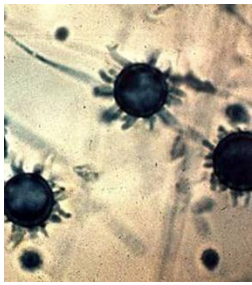
Case 2: Diff'l Diagnosis (cont)

- Lymphomas? - also presents with fever, night sweats, weight loss
  - 7-month illness without palpable lymph node enlargement or hepato-splenomegaly unusual (splenic abnormalities; but lymphadenopathy only later)
  - Short course of IV antibiotics gave transient improvement
- Parasitic/protozoal diseases?
  - Malaria: *P. vivax* or *P. ovale*
    - Multiple blood smears: negative
    - No typical fever paroxysms
  - Visceral leishmaniasis
    - Hepato-splenomegaly absent
    - VL fever would not respond to antibiotic therapy
  - Schistosomiasis
    - Exposure to fresh water in endemic region
    - But no eggs in stool samples



Case 2: Diff'l Diagnosis (cont)

- Rickettsial infection?
  - Q Fever: Extended fever without localizing symptoms
    - May cause culture-negative endocarditis (murmur), but EKG indicated no valve damage
    - No history of contact with animal placental tissues
- Fungal infection?
  - Histoplasmosis, blastomycosis, coccidioidomycosis possible
  - But would not improve with antibiotic treatment
- Bacterial infections?
  - Enteric Fever: *Salmonella typhi*
    - Usually resolve in within 4 weeks
    - Relapses are common but tend to be less severe than initial illness
  - Tularemia
    - Resolves within 4 to 5 weeks



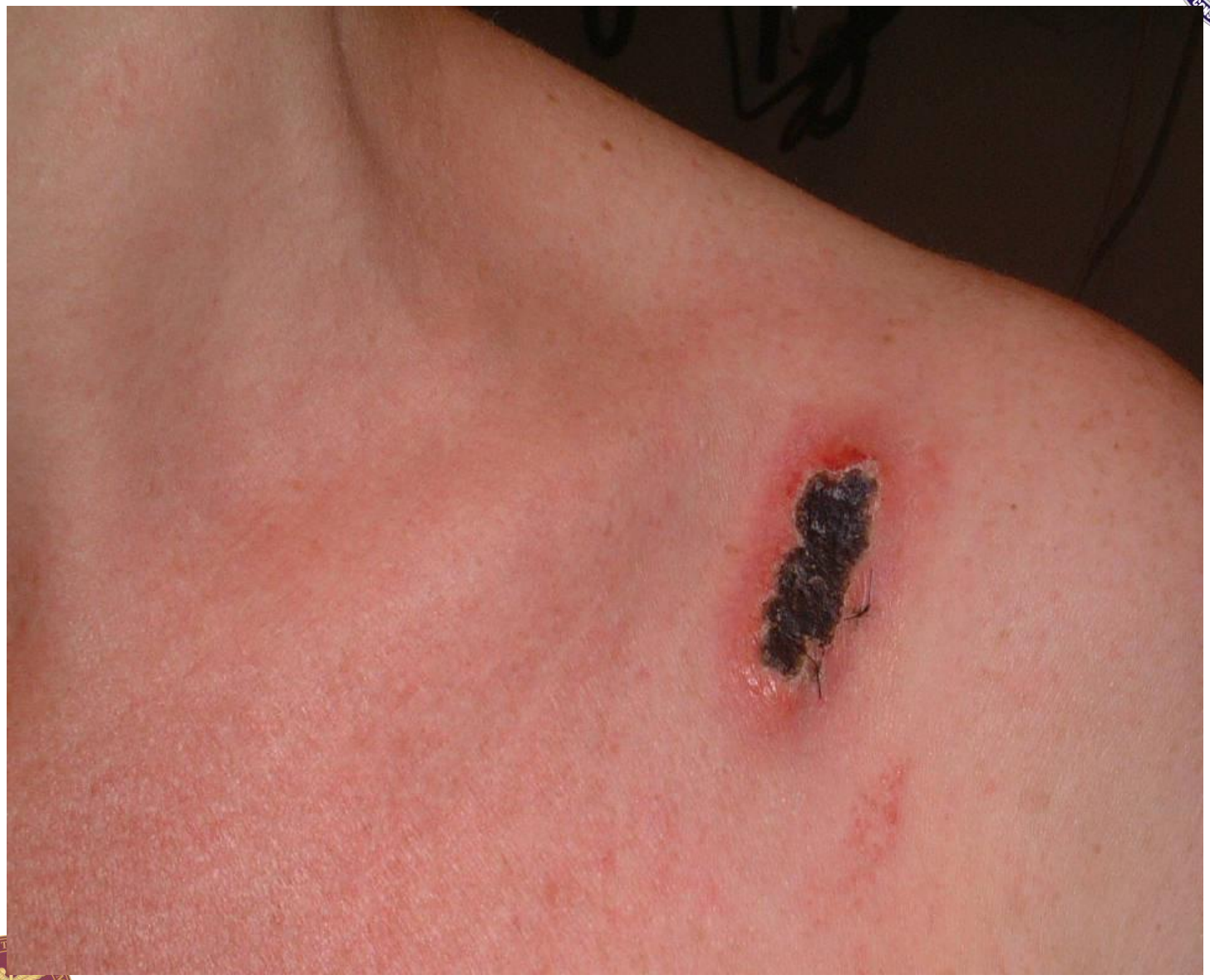
Case 2: Final diagnosis

- 37 Yo male with 3 weeks of intermittent fever and abdominal and back pain
- Chronic brucellosis with recent onset of sacroilitis
  - Raw milk consumption in endemic region
  - Untreated disease can persist for months, years
  - Back pain/sacroilitis
  - Biopsy of bone marrow; culture yielded *Brucella melitensis*

Case 3

- 35 yo female
- Co-worker opened a letter containing white powder a week earlier.
- The powder was checked by the FBI and was negative.
- She has a poorly healing lesion on her shoulder now.
- She has seen multiple physicians without a diagnosis.

Case 3



Case 3: Which could cause this?

- A – spider bite
- B – Leishmaniasis
- C – Anthrax
- D – Pseudomonas
- E – All of the above

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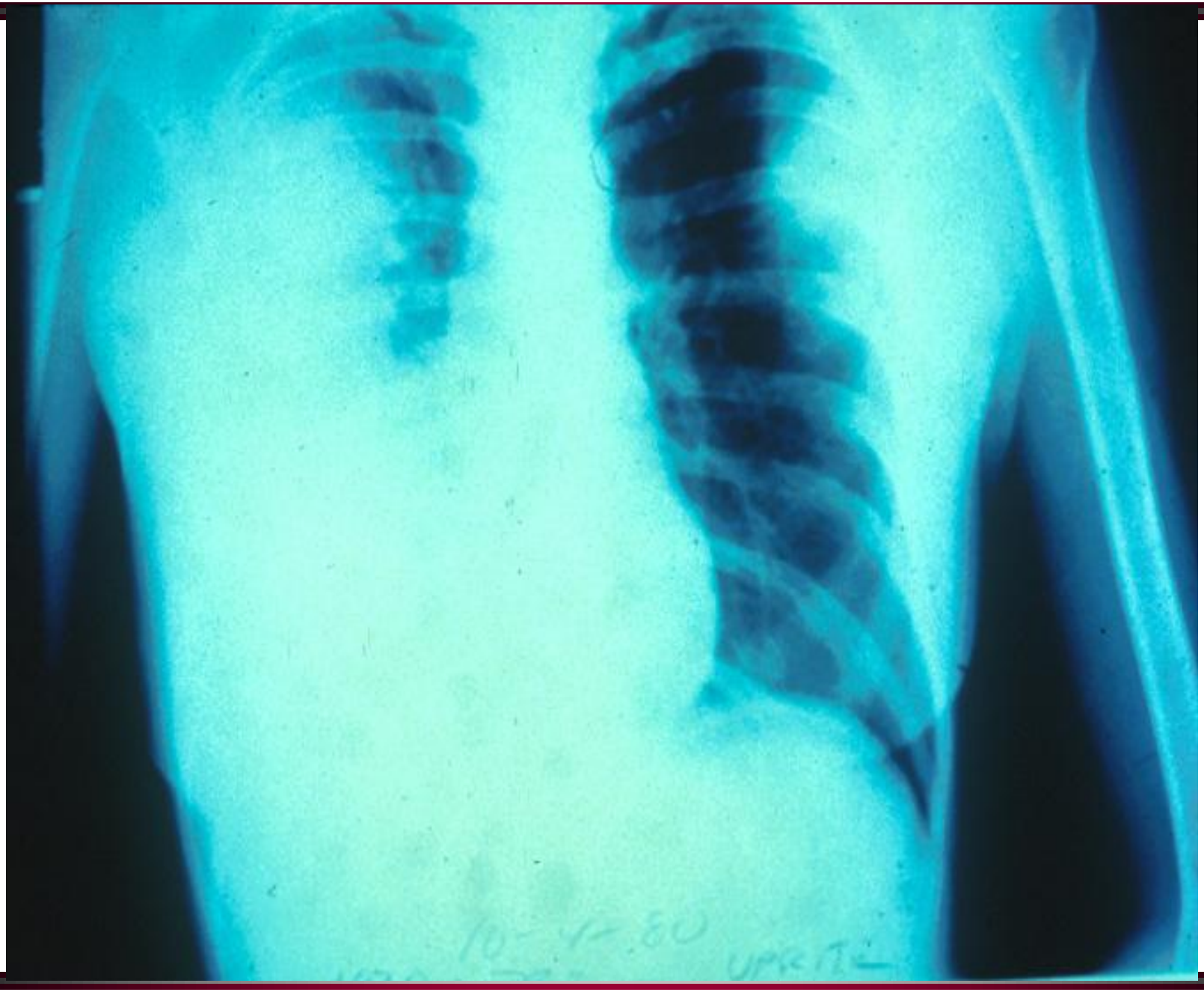
- A – spider bite
- B – Leishmaniasis
- C – Anthrax
- D – Pseudomonas
- E – All of the above

Case 3: Differential on black eschar

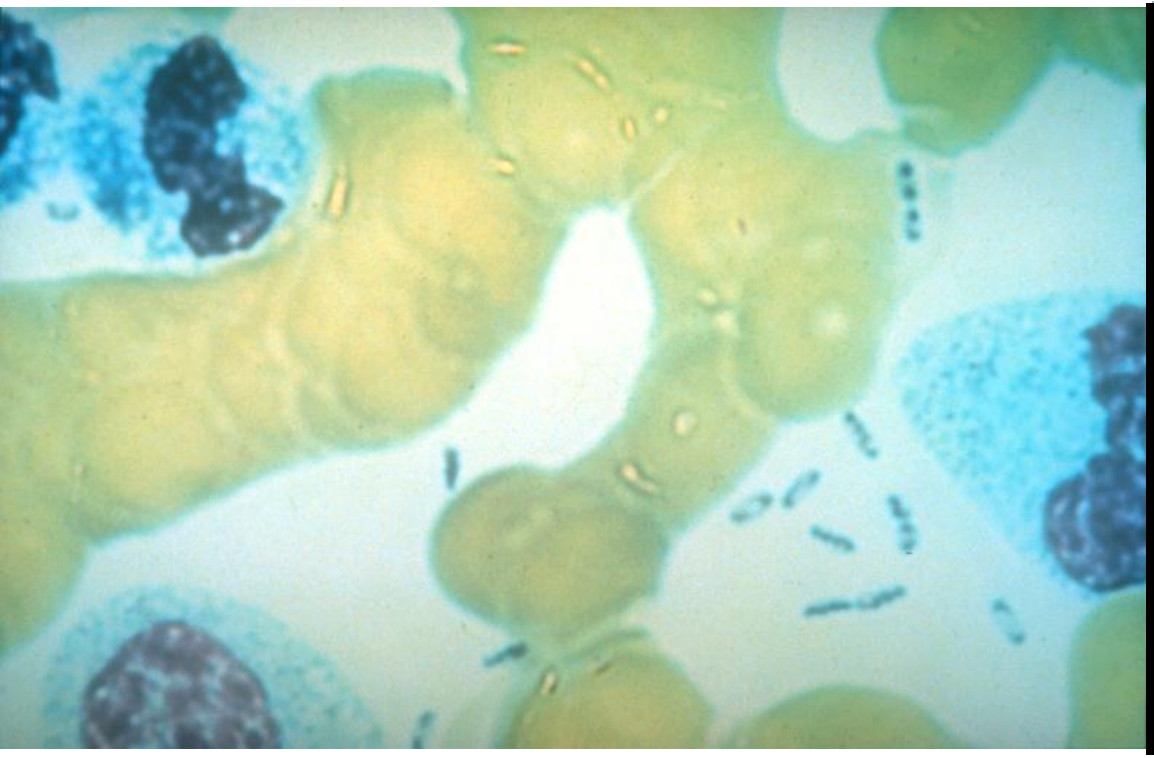
- Brown Recluse Spider bite
- Bacterial:
  - anthrax
  - tularemia
  - plague
  - cutaneous diphtheria
  - ecthyma gangrenosum
- Viral: Orf
- Fungal:
  - sporotrichosis
  - Aspergillus
  - Mucor
- Parasitic: cutaneous leishmaniasis
- Mycobacterial: TB and non-TB
- Rickettsiae
- Non-infectious: coumarin necrosis

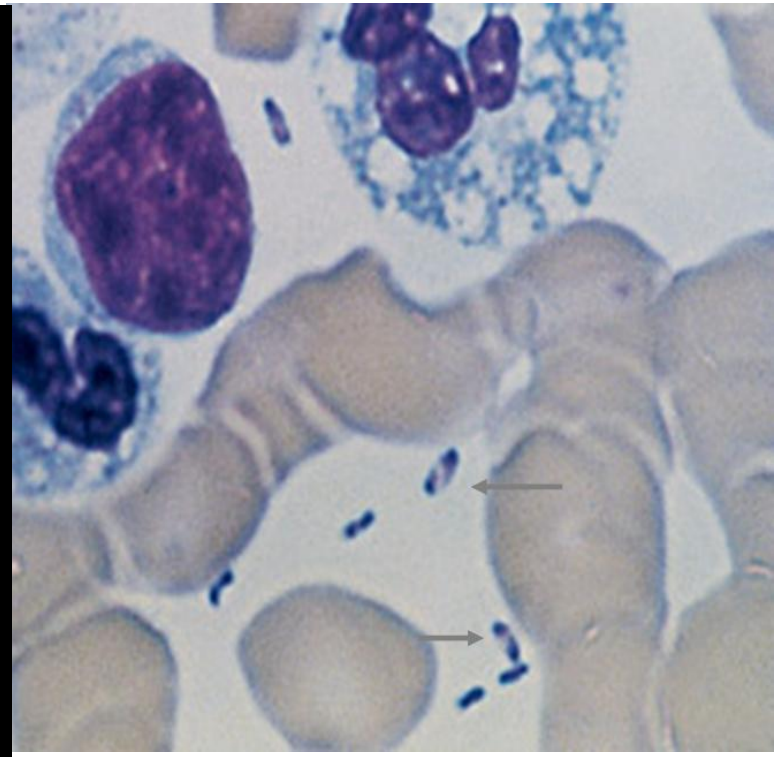
Case 3, continued

- Day 3:
  - high fever
  - shaking chills
  - headache
  - cough
  - dyspnea
  - myalgias



Blood Smears





European Tour
1347 - 1351

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